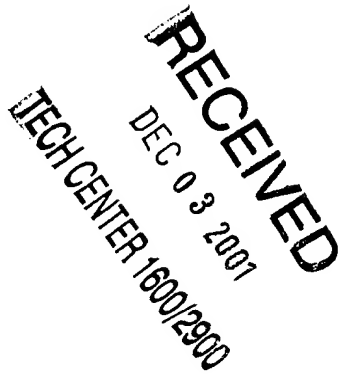
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Before the Board of Patent Appeals and Interferences



In re Patent Application of
von BORSTEL et al
Serial No. 08/460,186
Filed: June 2, 1996

Atty. Dkt. 1331-138
C#/M#
Group Art Unit: 1623
Examiner: Owens, H.
Date: November 30, 2001

Title: TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

☐	**NOTICE OF APPEAL** Applicant hereby appeals to the Board of Appeals from the decision dated _____ of the Examiner twice/finally rejecting claims _____ ($ 320.00)	$	0.00
☐	An appeal **BRIEF** is attached in triplicate in the pending appeal of the above-identified application ($ 320.00)	$	
☐	An **ORAL HEARING** is requested under Rule 194 ($280.00) (due within two months after Examiner's Answer)	$	0.00
☐	Credit for fees paid in prior appeal without decision on merits	-$ (	0.00)
☒	A supplemental reply brief is attached in triplicate under Rule 193(b)		**(no fee)**
☐	Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s) (**$110.00/1 month**; $400.00/2 months; **$920.00/3 months**; $1440.00/4 months)	$	0.00
	SUBTOTAL	$	0.00
☐	Applicant claims "Small entity" status; enter ½ of subtotal and subtract ☐ "Small entity" statement attached.	-$(	0.00)
	SUBTOTAL	$	0.00
	Less month extension previously paid on	-$(	0.00)
	TOTAL FEE ENCLOSED	$	0.00

Any future submission requiring an extension of time is hereby stated to include a petition for such time extension. The Commissioner is hereby authorized to charge any deficiency, or credit overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our **Account No. 14-1140.** A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty.: Leonard C. Mitchard, Reg. No. 29,009

Signature: _____

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In re Patent Application of
von BORSTEL et al
Serial No. **08/460,186**
Filed: **June 2, 1995**

Atty. Ref.: **1331-138**
Group: **1623**
Examiner: **Owens, H.**

For: **TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES**

* *

November 30, 2001

Honorable Commissioner of Patents
and Trademarks
Washington, DC 20231

SUPPLEMENTAL REPLY BRIEF

Sir:

This is supplemental to the Reply Brief filed September 25, 2001. The Reply Brief demonstrated that the Falcone, et al. publication does not teach that uridine phosphorylase inhibitors exert their beneficial effects by preventing the degradation of uridine to uracil. (Reply Brief, pages 7-8). However, it has recently come to the attention of appellants that Calabresi does address the issue of uracil toxicity. It is believed that it would be desirable to explain on the record why this teaching of Calabresi is insufficient to support an obviousness rejection.

Calabresi suggests that the mechanism of uridine toxicity may be related to degradation of uridine to uracil. Calabresi states:

> "While the exact mechanism by which Urd [uridine] induces its toxic effects in vivo is not known, Peters et al. have presented evidence that suggests that Urd toxicity in mice and rats might be related to the elevated plasma uracil concentrations induced by the catabolism of Urd." (Calabresi, et al., p. 2210, column 2, first full paragraph.)

The PTO has argued that it would have been obvious to combine one compound (an acyl uridine derivative) to increase plasma levels of uridine with a second compound (uridine phosphorylase inhibitor) to counteract toxicity associated with a metabolite of the first compound. (Examiner's Answer, page 7). Far from motivating the person of ordinary skill in the art to combine a uridine phosphorylase inhibitor with an acyl derivative of uridine, concerns about uracil toxicity would have suggested that it would be better to use a uridine phosphorylase inhibitor alone to achieve serum and tissue levels of uridine that are achievable without administering an acyl derivative of uridine. Calabresi discloses that:

> "By inhibiting Urd catabolism, the administration of BAU produces a dose-dependent and sustained increase in the concentration of Urd in plasma and tissues without evidence of Urd-related toxicity." (Calabresi, p. 2210, column 2, first full paragraph).

Rather than achieving a desired plasma level of uridine with an agent (an acyl derivative of uridine) that would be expected to result in uracil toxicity while attempting to mitigate such toxicity by also administering a uridine phosphorylase inhibitor, the person of ordinary skill in the art would have been motivated to achieve the same plasma levels of uridine by administering a uridine

phosphorylase inhibitor alone because that would completely avoid the problem of uracil toxicity associated with exogenous sources of uridine such as an acyl derivative of uridine.

Reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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By: _____

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